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USE OF ACE-INHIBITORS FOR THE PREVENTION OF DIABETES

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(57) Claim

Surprisingly it has now been found that ACE-inhibitors can reduce the morbidity rate of diabetes mellitus of metabolically normal patients having a diabetic risk, when administered orally in amounts, that do not have a significant influence on blood pressure. Metabolically normal non-diabetic patients having a diabetic risk are in particular such groups of patients, for which an increased morbidity rate of diabetes mellitus is to be expected because of an increased bodyweight and/or hereditary predisposition and/or other factors of influence.

1. A medical preparation for use as a preventative treatment against contracting diabetes for persons characterized as having a high probability of contracting diabetes from contracting diabetes comprising an angiotensin converting enzyme inhibitor.

5. A method of preventative treatment against contracting diabetes for persons characterized as having a high probability of contracting diabetes comprising the steps of:

providing the m dical preparation of claim 1, and

introducing said medical preparation int the body of the person b ing treated.

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Complete Specification for the Invention entitled:

"USE OF ACE-INHIBITORS FOR THE PREVENTION OF DIABETES"

The following statement is a full description of this invention, including the best method of performing it known to us:-

Use of ACE-Inhibitors for the Prevention of Diabetes

The present invention relates to the use of inhibitors of the angiotensin converting enzyme for the manufacture of a medicament for the prevention of diabetes in high-risk patients.

It is known, that inhibitors of the angiotensin converting enzyme (ACE) exhibit a strong hypotensive activity with hypertension in man. Such inhibitors previously have been isolated from the poison of the snake Bothrops jararaca and described as oligopeptides. The pentapeptide having the designation B.P.P.$_{5a}$ as well as the nonapeptide having the designation B.P.P.$_{9a}$ or SQ 20,881, the latter having the amino acid sequence pyroglu-trp-pro-arg-pro-gln-ile-pro-pro, have been shown to have a corresponding activity (see, The Lancet 1973, p. 72 and US patent 3,947,575). The prolin derivative having the chemical name 1-[(2S)-3-mercapto-2-methylpropionyl] -L-prolin, which is commercially available under the INN designation captopril, is such ACE-inhibitor, too.

Further ACE-inhibitors are sold under the trade names "Enalapril" (N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolin), "Lisinopril" and "Ramipril", or have been applied for registration with the drug administration ("Zofinopril").

The activity of the ACE-inhibitors is said to go back to a blocking of the enzyme, which, in the organism, converts angiotensin I into blood pressure active angiotensin II. The inhibitors have been used with great success with patients suffering from high blo d pressure, see New England Journal of Medicin , 1974, p. 817 as well as US patent 3,947,575.

Further it is known that the combined use of the ACE-inhibitor peptide B.P.P.$_{9a}$ or SQ 20,881 with certain extracts from plasma protein from young calves results in an improvement of wound healing obtained with such extracts. This means that the activity of the extracts is enhanced by the addition of the ACE-inhibitors. The activity may go back to an improvement of metabolism of unsufficiently supplied parts of tissue due to an enhanced uptake of glucose caused by the combination of the extracts with the ACE-inhibitors, whereby, specifically under diabetic metabolic conditions, blood circulation is improved and, upon local application, wound healing is enhanced, see DE-A-2,729,096 and DE-C-2,759,793.

Recently, ACE-inhibitors have been used as medicaments for the treatment of hypertensive conditions and cardiac insufficiency, as well as, in combination with extracts from deproteinized calf blood, for the treatment of circulatory and metabolic disorders.

Surprisingly it has now been found that ACE-inhibitors can reduce the morbidity rate of diabetes mellitus of metabolically normal patients having a diabetic risk, when administered orally in amounts, that do not have a significant influence on blood pressure. Metabolically normal non-diabetic patients having a diabetic risk are in particular such groups of patients, for which an increased morbidity rate of diabetes mellitus is to be expected because of an increased bodyweight and/or hereditary predisposition and/or other factors of influence. For example, for grossly overweight patients having an age of more than 50 years the risk of being affected by diabetes mellitus is about 45 %, based on a time period of two years. In such risk groups the intake of, e.g. 2 x 3 mg captopril per day, led to a reduction of this risk of m re than 50 %.

The treatment with the ACE-inhibit rs to b used in accordance with the invention is a mere preventive measure; the daily dose

of ACE-inhibitor is not sufficient for a significant influence on blood pressure. The administration of ACE-inhibitors also does not result in a lowering of the blood-sugar level and has no influence on the insulin secretion.

This activity of ACE-inhibitors on healthy people was not predictable since medicaments improving the glucose metabolism, such as sulfonyl ureas, biguanides or insulin, are not suitable for such preventive treatment. For example, the administration of sulfonyl ureas has an influence on the insulin secretion and in addition would result in a weight increase, i.e. the weight problems of patients of this risk group would be enhanced.

For the use according to this invention the ACE-inhibitors are administered orally in amounts of 0.5 to 15 mg/d, preferably in amounts of 1 bis 10 mg/d. A typical dose for an overweight adult is, e.g. 2 x 3 mg captopril per day, however, the dose may vary depending on the bodyweight, age and physical condition of the patient, in the usual way.

For the use according to the invention the active ingredient is formulated with conventional inactive ingredients and carriers, which generally are used for oral applications. Thus, a single dose preferably is in the range of 0.5 to 10 mg, more preferably 1 to 5 mg, ACE-inhibitor.

On the other hand, for the treatment of high blood pressure, the daily dose of captopril is, e.g., 25 mg to 150 mg per day; thus it is much higher than the daily amount necessary for the diabetes prevention.

The diabetes preventive activity of ACE-inhibitors can be seen from the following study and its results, which has been carried out with captopril.

Experimental report

122 overweight people having an average overweight of 25 % and a disturbed oral glucose tolerance were selected. These patients gave their informed consent to take part in this study over three years. All of them had 5 to 10 trials of weight reduction, which all were without success. In these patients, a diabetes mellitus according to the definition of The World Health Organization-Report (Technical Report Series 646, 1-80, 1980) could be excluded. They were divided into two equal groups so that there was no difference with respect to age, degree of impairment according to the glucose tolerance test (OGTT) and degree and duration of overweight. The patients were ambulantly controlled in half year intervals. As at the beginning the following blood data were taken at these controls: blood sedimentation, blood count, fasting blood sugar, OGTT, weight, cholesterin and triglycerides, serum glutamate oxalate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT). Thereby, diseases impairing metabolism were excluded.

The first group received 2 x 3 mg captopril per day, the second placebo accordingly. The patients were obliged to take no medicaments impairing metabolism, e.g. diuretics, ß-blockers, or the like. Within 3 years, in both groups 28 patients were eliminated for different reasons. This did not change the groups in a way preventing a statistical evaluation.

Applying Students t-tests (Snedecor, G.W.; Cochran. W.E.: Statistical Methods, II. Edition, Ames Iowa: Iowa-State, University-Press, 1967), the Mantel-Haenszel-equation (Mantel, N.: J. Am. Stat. Ass. 58: 690-700 (1963), Miettinen, O.: Am. J. Epidemol. 103: 226-235 (1976)) and Pitman's permutation test (Bradley, J.V. Distributi n-free Statistical Tests. Englewood Cliffs, New Jersey: Prentice-Hall 1968, 68-86) and taking into consideration the present variables: hypertriglyceridemia and

family diabetes affliction, for the captopril group a significant lower morbidity rate for diabetes mellitus was found ($p < 0.001$; Student's t-test).

The results of the study are shown in the following table.

Morbidity rate on Diabetes mellitus with overweight women[a] under captopril (C)[b] compared to placebo

Period of time		1985 -1	1986 - 2	1987 - 2	1988 - 1
Number	C	63	60	54	48
	P	59	54	49	46
Age	C	55,3 ± 0,8	56,2 ± 0,9	57,4 ± 0,9	58,6 ± 1,0
(years)	P	57,2 ± 1,1	58,4 ± 1,0	59,6 ± 1,3	60,3 ± 1,3
Weight	C	126,0 ± 1,1	124,1 ± 1,6	125,2 ± 1,1	125,5 ± 1,6
(in % of ideal body weight[c])	P	124,1 ± 1,3	136.0 ± 1,4	123,6 ± 2,1	124,1 ± 1,9
Diabetes	C	0	2	4	4
mellitus[d]	P	0	3	6	11[e]

a with impairment according to OGTT; no diabetogenic medicaments

b 2 x 3 mg per day

c ideal weight: body height (cm)-100-15 %

d WHO-report: Techn. Rep. Ser. 646, 1-80 (1980)

e Significance at $p < 0.001$; Student's t-test. Calculation acc rding to Mantel-Haenszel[1] and Miettinen[2] and remaining constant when taking hypertriglyceridemia and family diabetes affliction into consideration[3].

1 Mantel, N.J.Am.Stat.Aam. 58: 690-00 (1963)

2 Miettinen,O., Am.J.Epidemiol. 103: 226-235 (1963)

3 Bradley,J.V., Distribution-free statistical tests. Englewood Cliffs, New Jersey: Prentice-Hall 1968, 68-86.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A medical preparation for use as a preventative treatment against contracting diabetes for persons characterized as having a high probability of contracting diabetes from contracting diabetes comprising an angiotensin converting enzyme inhibitor.

2. A medical preparation according to claim 1 wherein the angiotensin converting enzyme inhibitor is present in an amount of between 0.5 mg and 10 mg per dose unit.

3. A method of producing a medical preparation for use as a preventative treatment against contracting diabetes for persons characterized as having a high probability of contracting diabetes from contracting diabetes comprising the step of including an angiotensin converting enzyme inhibitor.

4. A method according to claim 3 wherein the angiotensin converting enzyme inhibitor is present in an amount of between 0.5 mg and 10 mg per dose unit.

5. A method of preventative treatment against contracting diab tes for persons characterized as having a high probability of contracting diabetes comprising the steps of:

providing the medical preparation of claim 1, and

introducing said medical preparation into the body of the person being treated.

6. The method according to claim 3 wherein the medical preparation is introduced to the body of the person being treated by oral ingestion.

7. A medical preparation in accordance with claim 1 substantially as herein described with reference to the examples.

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